Prognostic impact of definitive local therapy of the primary tumor in men with metastatic prostate cancer at diagnosis; a population-based, propensity score analysis.

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Purpose

- This study investigated whether definitive local therapy (radical prostatectomy or brachytherapy) of the primary tumor improves survival in men with metastatic prostate cancer at diagnosis.

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Background & Significance

- Optimal treatment for metastatic prostate cancer (mPrCA) remains a clinical dilemma.

- Systemic therapy, typically androgen ablation is used to treat men diagnosed with mPrCA while definitive local therapy is often reserved for organ confined disease.

- Definitive local therapy such as radical prostatectomy or brachytherapy may suppress systemic disease progression and improve survival

Methods

- **Data source**: SEER 2004-2010, follow-up to Dec 31, 2012

- **Inclusion criteria**:

1. Age 35 years or older

2. Must have pathological or radiological confirmation of metastasis as identified by the SEER variable “collaborative staging metastasis at diagnosis”.

3. Must have documented stage IV metastasis at time of diagnosis as defined by AJCC
    i. M1a - *cancer metastasis to lymph nodes beyond regional lymph nodes*
    ii. M1b - *bone metastasis*
    iii. M1c - *metastasis to other sites with or without bone disease*

4. Must have PrCA listed as the first and only primary tumor.

Methods

- Definition of definitive local therapy
  1. Radical prostatectomy (RP)
  2. Brachytherapy (BT)
     - Radioactive implants
     - Radioisotope therapy
     - Any combination of radioactive implants, radioisotopes therapy and external beam radiation
  3. No definitive local therapy (NDLT)

- Outcome measures
  1. All-cause mortality
  2. Prostate cancer-specific mortality

Methods

- **Covariates**: age, race, marital status, tumor grade (Gleason sum), PSA level at diagnosis, and cancer registry.

- **Statistical analysis**:
  - Kaplan-Meier survival curves
  - Conventional multivariable Cox proportional hazard regression models
  - Propensity score-adjusted Cox proportional hazard regression
  - Estimation of propensity scores: multinomial logistic regression with treatment a 3-level variable conditioned on covariates.
  - Propensity scores used as a linear term and also categorized into quintiles

Results

Table 1: Descriptive statistics (n= 7858)

Characteristic		No RP or BT N = 7516 (95.7%)	RP N = 222 (2.8%)	BT N = 120 (1.5%)	χ^2 P-value
		N (%)	N (%)	N (%)	
Vital status					
	Alive	3278 (43.6)	182 **(82.0)**	80 (66.7)	<0.0001
	Dead	4238 (56.4)	40 (18.0)	40 (33.3)	
PrCA-specific mortality					
	Alive/death from other causes	4104 (54.6)	188 **(84.7)**	86 (71.7)	<0.0001
	Death from prostate cancer	3412 (45.4)	34 (15.3)	34 (28.3)	
Age					
	< 65 years	2305 (30.7)	142 (64.0)	40 (33.3)	<0.0001
	≥ 65 years	5211 **(69.3)**	80 (36.0)	80 (66.7)	
Race					
	White	5469 (72.8)	168 (75.7)	83 (69.2)	0.4935
	Black	1477 (19.6)	39 (17.6)	28 (23.3)	
	Other	461 (6.1)	14 (6.3)	9 (7.5)	
	Unknown	109 (1.5)	1 (0.4)	0 (0)	
Marital status					
	Married	4198 (55.9)	172 **(77.5)**	78 (65.0)	<0.0001
	Single	1138 (15.1)	18 (8.1)	16 (13.3)	
	Separated/divorced/widowed	1589 (21.1)	20 (9.0)	16 (13.3)	
	Unknown	591 (7.9)	12 (5.4)	10 (8.3)	

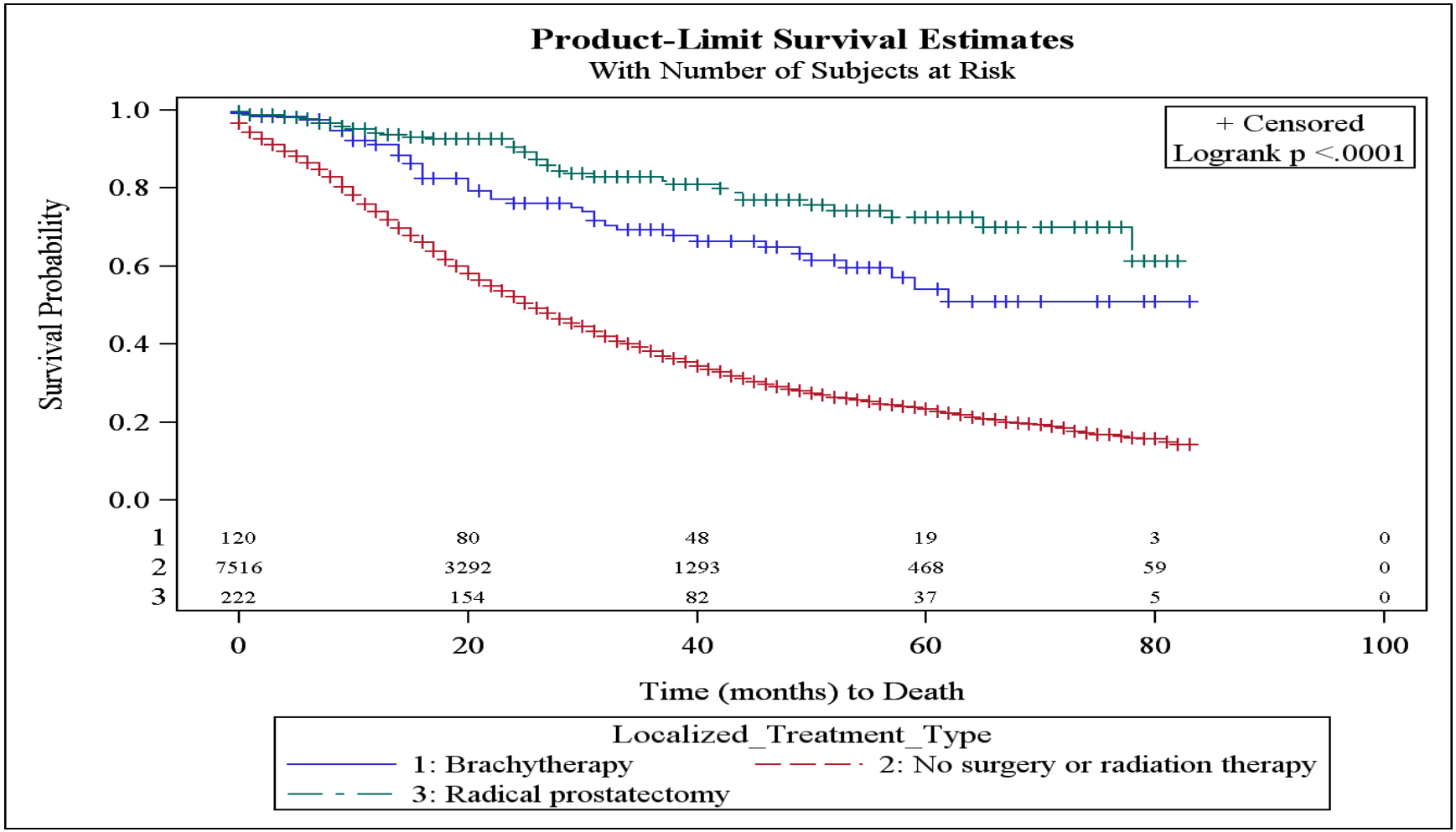
Results

Table 1: Descriptive statistics (n = 7858)

Characteristic		No RP or BT N = 7516 (95.7%)	RP N = 222 (2.8%)	BT N = 120 (1.5%)	χ^2 P-value
		N (%)	N (%)	N (%)	
Tumor grade (Gleason sum)					
	Well differentiated (≤ 4)	8 (0.1)	3 (1.4)	1 (0.8)	<0.0001
	Moderately differentiated (5-6)	383 (5.1)	36 (16.2)	21 (17.5)	
	Poorly differentiated (≥ 7)	5433 (72.3)	175 **(78.8)**	85 (70.8)	
	Undetermined/unknown	1692 (22.5)	8 (3.6)	13 (10.8)	
PSA category					
	Normal (0-4 ng/ml)	75 (1.0)	10 (4.5)	4 (3.3)	0.1246
	Borderline (5-9 ng/ml)	14 (0.2)	0 (0.0)	0 (0.0)	
	Elevated (≥ 10 ng/ml)	6805 (90.5)	195 (87.8)	109 (90.8)	
	Not done/unknown	622 (8.3)	17 (7.7)	7 (5.8)	
AJCC M stage					
	M1a	433 (5.8)	20 (9.0)	18 **(15.0)**	<0.0001
	M1b	5264 **(70.0)**	139 (62.6)	68 (56.7)	
	M1c	1819 (24.2)	63 (28.4)	34 (28.3)	
External beam radiation					
	No	7516 (100)	188 **(84.7)**	69 (57.5)	<0.0001
	Yes	0	34 (15.3)	51 (42.5)	

Results

Kaplan-Meier survival curves for all-cause mortality



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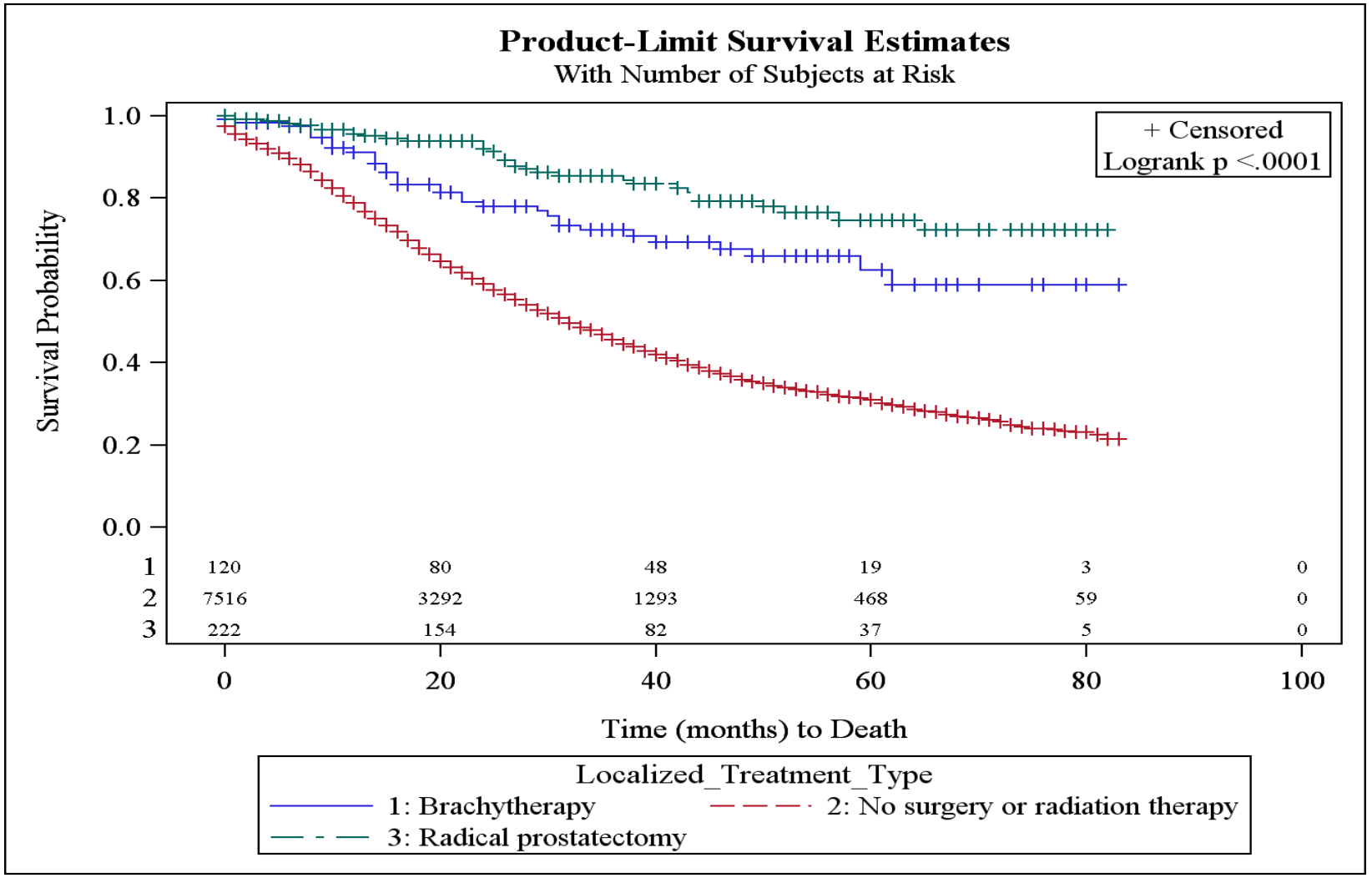
Results Kaplan-Meier survival curves for PrCA-specific mortality



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Results

Table 2: Probability of death after diagnosis with metastatic prostate cancer (N = 7858) – Conventional Cox PH model.

Characteristic	N	All-cause mortality		Prostate cancer-specific mortality	
		Crude HR (95% CI)	Adjusted HR [a] (95% CI)	Crude HR (95% CI)	Adjusted HR [a] (95% CI)
Treatment type					
No definitive local therapy	7516	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Radical prostatectomy	222	0.21 (0.15-0.29)	**0.27** (0.20-0.38)	0.22 (0.16-0.31)	**0.28** (0.20-0.39)
Brachytherapy	120	0.38 (0.28-0.53)	**0.43** (0.31-0.59)	0.40 (0.29-0.57)	**0.46** (0.33-0.64)

[a] Adjusted for age, race, marital status, tumor grade, prostate-specific antigen level, and cancer registry.

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Results

Table 3: PrCA-specific mortality - propensity score-adjusted analyses (N = 7858)

Model		Treatment type	N	Adjusted HR (95% CI)
Propensity score-adjusted (linear term)		NDLT	7516	1.0 (ref)
		RP	222	**0.22** (0.17-0.28)
		BT	120	**0.40** (0.32-0.51)
Propensity score-adjusted (quintiles)		NDLT	7516	1.0 (ref)
		RP	222	**0.22** (0.18-0.28)
		BT	120	**0.39** (0.31-0.49)
Propensity score-adjusted subset analysis				
AJCC M stage				
	M1a	NDLT	433	1.0 (ref)
		RP	20	**0.18** (0.07-0.50)
		BT	18	**0.29** (0.13-0.64)
	M1b	NDLT	5264	1.0 (ref)
		RP	139	**0.22** (0.16-0.30)
		BT	68	**0.49** (0.36-0.67)
	M1c	NDLT	1819	1.0 (ref)
		RP	63	**0.23** (0.16-0.35)
		BT	34	**0.36** (0.24-0.54)

Discussion

- Men presenting with metastatic PrCA at diagnosis who undergo definitive local therapy have better survival outcomes than those who do not.

- Limitations
  - Treatment selection bias
    - Better survival due to better prognosis of those who underwent definitive therapy due to other reasons
  - Possibility of confounding by receipt of systemic therapies
  - Confounding by unmeasured factors:
    - comorbidities, diet, physical activity, BMI/adiposity, smoking status…..

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